Rejection of Claims 1-18 Under 35 U.S.C. §112, first paragraph

Claims 1-18 stand rejected under 35 U.S.C. §112, second paragraph as allegedly lacking enablement. Applicants respectfully traverse the rejection.

Claims 1-6 and 9-15 recite methods for inhibiting the proliferation of mammalian cells that express an A_{2B} adenosine receptor comprising administering a therapeutically effective amount of an A_{2B} adenosine receptor antagonist to the mammalian cells. The A_{2B} adenosine receptor antagonist can be, for example, a non-selective or selective adenosine receptor antagonist. Claims 16-18 recite, *inter alia*, methods of assaying compounds to determine if they are A_{2B} receptor antagonists or agonists.

The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. "The determination of what constitutes undue experimentation is a given case requires the application of a standard of reasonableness, having due regard of the nature of the invention and the state of the art." *In re Wa*nds, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ansul Co. v. Uniroyal, Inc.*, 169 U.S.P.Q. 759, 762-63 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*

The Office Action recognizes that the specification is enabling for the design and administration of A_{2B} antagonists to cells in culture, however, the Office Action asserts that the

specification is not enabled for the design and administration of A_{2B} antagonists to cells in whole organisms with an expectation of success.

The Office Action alleges that the prior art does not teach that HREC cell culture is a substantial art recognized model for the claimed invention, so that one of skill in the art would expect a correlation between HREC *in vitro* cell effects and effects *in vivo*. The Office Action states that at the time the invention was made, administration of A_{2B} antagonists to the retina *in vivo* would have had many considerations not accounted for by a particular cell in cell culture that is stabilized at one stage. The Office Action thus concludes that the specification does not enable claims drawn to the administration of A_{2B} antagonists *in vivo*.

Applicants respectfully disagree with the Office Action and assert that the HREC model is a valid model for *in vivo* activity as claimed. In addition to the HREC model, a mouse pup model of oxygen-induced retinopathy has been used to demonstrate the effects of AdoR antagonists on neovascularization. *See*, Mino *et al.*, Adenosine receptor antagonists and retinal neovascularization *in vivo*. Invest. Ophthalmol. Vis. Sci., 42:3320 (Mino (a); copy attached). The use of this mouse model was described in the specification at page 5, lines 22 through page 6, line 1. Mino (a) tested the following AdoR antagonists in the *in vivo* mouse pup model:

Antagonist	Antagonist Type	Effect on Retinal Neovascularization
Xanthine amine congener (XAC)	Non-selective AdoR antagonist	Significant reduction
ZM241385	A_{2A} selective antagonist	No effect
3-N-propylxanthine (enprofylline)	A_{2B} selective antagonist	Significant reduction
3-isobutyl-8-pyrrolikeinoxanthine (IPDX)	A_{2B} selective antagonist	Significant reduction
Cyclopentyl-1,3-diproprylxanthine (CPX)	A_1 selective antagonist	No effect

The results demonstrated that non-selective AdoR antagonists and A_{2B} selective antagonists reduced proliferation of cells in the retina, as disclosed and described in the specification.

Therefore, as demonstrated by the *in vitro* HREC model and the *in vivo* mouse pup model, selective and non-selective A_{2B} antagonists operate *in vitro* and *in vivo* to reduce proliferation of cells, just as described and disclosed by the specification. Additionally, the teachings of the specification and Mino (a) demonstrate that A_{2B} antagonists can indeed be administered to cells in a whole organism. Mino (a) teaches that A_{2B} antagonists administered intraperitoneally to a whole organism were active in retinal cells. Therefore, the specification provides enablement for methods of inhibiting or reducing proliferation of mammalian cells that express an A_{2B} adenosine receptor in whole organisms.

The Office Action further alleges that:

> specific A_{2B} agonists and antagonists were not available in the prior art by traditional design methods taught by Klotz *et al.* and Kim *et al.* for instance. These references taught that a specific agonist and/or antagonist of the A_{2B} isoform was still needed (Klotz p. 5 and p.8, Col. A; Kim p. 2835, col. B.). The instant specification does not teach any specific A_{2B} isoforms that are know to be useful for *in vivo* administration for the proliferation of cells *in vivo* [as] claimed. See Office Action, page 4, first full paragraph.

Initially, the Office refers to "specific" and "non-specific" A_{2B} agonists and antagonists. However, the terms used in the art to describe A_{2B} agonists and antagonists are "selective" and "non-selective." See e.g., Kim, Klotz, and specification page 6, lines 11-14. Next, the references cited by the Office as teaching that A_{2B} agonists and antagonists were not available in the prior art are from 1998, three years before the filing of the instant application. The specification teaches and the Office recognizes that at the time of the filing of the application, A_{2B} agonists and antagonists were know. In fact, the Office Action states:

> The specification as filed teaches by way of example administration of the A_{2B} antagonists JW-V1-08 and 3-N-propylxanthine (selective) and NECA (non-selective) in human retinal endothelial cells (HREC cells) in culture. See Office Action, page 3, first full paragraph.

As conceded by the Office, A_{2B} selective and non-selective antagonists were clearly known in the art at the relevant time, that is, at the time of filing of the application. The methods by which the antagonists and agonists were or are to be discovered, i.e., by "traditional design methods" is of no importance.

The Office Action alleges that the specification does not teach any A_{2B} antagonists that were known to be useful for *in vivo* administration. The specification, however, teaches that A_{2B} antagonists such as 3-N-propylxanthine (see e.g., page 9, lines 24-26) and xanthine amine congener (see e.g., page 10, lines 3-12) are useful in the methods of the invention. Mino (a), as described above, demonstrates that these A_{2B} antagonists are indeed useful *in vivo* to reduce or inhibit the proliferation of mammalian cells *in vivo*.

Regarding claims 16-18, the Office Action asserts that the claims recite assay methods that read on administration to retinal endothelial cells *in vivo* and alleges that such administration is not enabled by the specification. The specification, however, teaches that one example of such

an assay is an *in vivo* mouse pup model of oxygen induced retinopathy. See page 5, lines 22 through page 6, line 1. This model can be used to screen for A_{2B} antagonists and agonists. Mino (a) demonstrates that such *in vivo* assays do indeed function as disclosed by the specification. The specification therefore enables the *in vivo* assays of A_{2B} adenosine receptor antagonists and agonists.

Claims 7 and 8 recite methods for inhibiting proliferation of mammalian cells that express an A_{2B} adenosine receptor comprising administering a therapeutically effective amount of an A_{2B} adenosine receptor antisense oligonucleotide or an A_{2B}-specific ribozyme. The Office Action asserts that there is a high level of unpredictability in the antisense and ribozyme art, and in particular in the delivery of such therapeutic molecules *in vivo*. The Office Action asserts that the specification does not teach stability of the molecules *in vivo*, effective delivery to the whole organism, specificity to target tissues, dosage, toxicity, and entry of the molecule into a cell and effective action therein.

The specification teaches that ribozymes and antisense molecules can be successfully delivered *in vivo* to reduce or inhibit proliferation of mammalian cells that express an A_{2B} adenosine receptor. *See e.g.*, specification page 6, lines 15-26. Dosages and administration is taught at, *inter alia*, page 8, lines 2-27.

Additionally, Mino, *et al.*, "*Adenosine A_{2B} Receptor Inhibition Decreases Retinal Neovascularization in Mice with Oxygen Induced Retinopathy*", *IOVS*, 2000 (Mino (b)); of record; copy attached for Examiner's convenience) demonstrates the successful delivery of a ribozyme targeted to adenosine A_{2B} receptor *in vivo* in the mouse pup model of oxygen-induced retinopathy. The ribozyme was stable *in vivo*, was effectively delivered to the whole organism, a

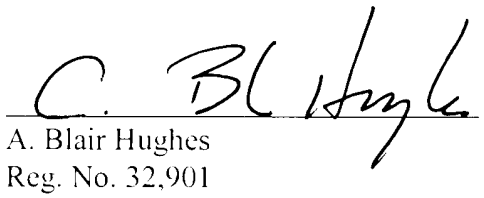
mouse in this case, was specifically delivered to a target tissue, retinal cells in this case, and was effective to decrease retinal neovascularization.

Therefore, just as taught by the specification, oligonucleotide molecules such as antisense molecules and ribozymes can be used successfully *in vivo* to inhibit the proliferation of mammalian cells that express an A_{2B} adenosine receptor. Claims 7 and 8 are therefore enabled by the specification.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

Date: February 10, 2003

By: 

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APPENDIX A

Marked-Up Version of Claims to Show Changes Made

16. (Amended) A method for assaying compounds to determine if they are A_{2B} adenosine receptor antagonists or A_{2B} adenosine receptor agonists comprising the steps of:

    a. preparing a first and second sample of [human] retinal endothelial cells;

    b. adding a compound to be tested to the first sample of [human] retinal endothelial cells and allowing the compound to remain in contact with the first sample of [human] retinal endothelial cells for a defined period of time; and

    c. comparing the number of new cells grown in the first sample with the number of new cells grown in the second sample.

19. (New) The method of claim 16, wherein the retinal endothelial cells are human cells.